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CONTRACTING ORGANIZATION: University of Y ä & } • ä
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REPORT DATE: R | ˇ Á € FH

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S) David Rabago, M.D. E-Mail: david.rabago@fammed.wisc.edu				5d. PROJECT NUMBER	
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14. ABSTRACT The purpose of this research effort is to conduct a randomized controlled trial (RCT): "Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness" which will evaluate the effects of two different types of nasal irrigation solution compared to a control group for sinus and fatigue symptoms in adults with GWI. The primary activities conducted during year two of the project involved obtaining all necessary approvals from required regulatory bodies, coordination with the Madison Veterans Affairs Hospital (VA) for subject identification and recruitment, refinement of the study database structure, procurement of study materials (neti pots, xylitol, saline), and subject recruitment and enrollment.					
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a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION

More than 50,000 troops returned from the Persian Gulf conflicts reporting a myriad of medically unexplained symptoms with no identifiable etiology. While patients who meet the case definition of Gulf War Illness (GWI) can have a myriad of symptoms, two of the most prevalent and debilitating ones are chronic nasal congestion and fatigue. The purpose of this research effort is to conduct a randomized controlled trial (RCT): “Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness” which will evaluate the effects of two different types of nasal irrigation solution compared to a control group for sinus and fatigue symptoms in adults with GWI.

BODY

The major objectives of the study are twofold: 1) To find an effective adjunctive therapy for veterans with Gulf War Illness (GWI) and symptoms of chronic rhinosinusitis (CRS) and fatigue and 2) To evaluate the proinflammatory bias of each individual’s profile at baseline and in response to therapy. Statistically positive results on clinical outcome measures would demonstrate that nasal irrigation (NI) can provide effective adjunctive therapy for CRS and fatigue, improving quality of life for GWI-affected patients and potentially to society through reduced use of medical resources use and absenteeism. Positive findings on cytokine and cellular assessment would shed light on the etiology of CRS and fatigue in the GWI population and contribute to the understanding of each; positive response to therapy would elucidate a biological mechanism of action of NI. Finally, the finding that NI, adjunctive to routine care, is more cost effective than “routine care only” would provide economic justification for its clinical use in the studied population.

The primary activities conducted during year two of the project involved the approval process for human subjects research, coordination with the Madison Veteran Affairs Hospital (VA) for subject identification and recruitment, refinement of the study database structure, procurement of study materials (neti pots, xylitol, saline), and subject recruitment and enrollment.

The human subjects research approval process required protocol submission to the UW Health Sciences Institutional Review Board (HS IRB) and the Madison Veteran Affairs Research and Development (VA R&D) Committee. In order to proceed with human subjects research, both the UW IRB and the VA R&D require completion of separate, yet concurrent, research review and approval processes. The HS IRB review process involves submission of an on-line application submitted through the Application Review for Research Oversight at Wisconsin (ARROW) system. The initial HS IRB application was submitted on 11/25/11 and approval was granted on 7/23/12 following final endorsement by the VA R&D Committee. A continuing review submitted to the HS IRB on 4/22/2013 was approved on 05/20/2013. The initial VA R&D Committee application submitted on 11/25/11 was also approved on 7/10/12.

The company that provided xylitol (Danisco) is now owned by a private company (DuPont) a large multinational corporation which has its own human subjects review process. The PI has been in active communication with Danisco-Dupont regarding continuity of study as well as procurement and packaging of xylitol packets (sachets) for individual use by participants in the xylitol arm of the study. These communications have been positive and the study remains a

priority of Danisco-Dupont. The study approval was obtained on 08/13/2012 following a teleconference with the PI, study personnel and the Dupont Human Studies Committee (DHSC).

The U.S. Food and Drug Administration (FDA) guidance regarding the use of nasal irrigation has changed during the ramp-up period of the current study. Heightened awareness of potential harms has necessitated a change in protocol. The PI also sought input on the need for an Investigational New Drug (IND) application for xylitol. The opinion of senior University or Wisconsin legal and pharmacy staff was that an IND number is needed for this study. Therefore, while not identified as a requirement through the human subjects research approval process, the PI elected to submit an IND application to the FDA for the use of xylitol. Originally developed as a food supplement, xylitol will be tested for its efficacy relating to symptoms of fatigue and rhinosinusitis. The IND application was submitted on 08/20/2012 and there were no deficiencies identified with this application (IND116364).

The study also obtained necessary approvals from the FDA and the USAMRMC/Human Research Protections Office prior to commencement of subject enrollment and patient-related study activities.

Regarding the procurement of xylitol, its manufacturer (Danisco/Dupont) has provided xylitol in daily use packets at no cost as indicated in the protocol and letter of support in the initial grant application.

The study design for initial subject identification is the utilization of an ICD-9 code screen. Drs. Bridges and Rabago have experience with this strategy in the VA and UW Hospitals and Clinics contexts respectively. We were to a) identify veterans who were in the first Gulf War and b) search the ICD-9 coding record to identify those with appropriate diagnoses: CRS (473.*) or fatigue (780.7). Because multiple episodes of acute rhinosinusitis are the most common risk factor for, and can suggest the presence of CRS, we will also screen the ICD-9 database for 2 or more episodes of acute sinusitis (code: 461.9) in the past two years. The first round of ICD-9 queries for sinus and fatigue symptoms in Gulf War Veterans in the local area returned an index of only 34 people. A larger pool of additional potential subjects was identified in a broader query. As potential subjects are identified, we conduct outreach through mailings. Of the initial screen, 8 potential subjects have been contacted and screened by phone and are potentially eligible. We are currently scheduling in-person screening evaluations and 4 participants have been enrolled till date.

As a means to increase the subject pool, an expanded protocol was submitted and approved by the UW Health Sciences IRB. The protocol included community recruitment methods such as tear-off flyers in public places veterans might frequent, presentations of study information to VFW and other veterans groups and electronic informational advertisements to be posted on VFW websites and listservs. These identifications methods are designed to identify veterans who receive care outside the VA system. Till date, 5 eligible participants have been identified through the community recruitment methods and we are currently scheduling in-person screening evaluations. The table below is a summary of eligible and/or enrolled subjects recruited from the VA and the community during the reporting period.

	VA Recruitment	Community Recruitment	Total
Eligible subjects	8	5	13
Enrolled subjects	4	0	4

Study team members have had meetings with staff associated with the UW Clinical Research Unit (CRU) to review clinical services to be utilized by the study as well as the Pharmaceutical Research Center (PRC) which will be housing and dispensing all study medications (Xylitol and Saline). We have final approval on all procedures associated with these two entities and have begun enrolling and scheduling subjects. Study team members will continue to meet with CRU & PRC as study activities progress.

Study personnel have also been meeting regularly with DFM data personnel to develop the tracking database for study participants based on the course of study activities. The database will continue to be modified as the protocol proceeds through the human subjects recruitment and enrollment process.

Difficulties with the study relate to the human subject research approval process. Due to the complexity of engaging in human subjects research with veterans, the approval process has resulted in a more complicated progression of study activities. The complexity of this process was compounded by the unanticipated addition of the owner (DuPont) of the Xylitol manufacturing company (Danisco) and its human subjects research approval process early in the study ramp up.

KEY RESEARCH ACCOMPLISHMENTS:

- Study approval from all relevant stakeholders (UW HS IRB, VA R & D Committee, DHSC)
- Expansion of recruitment strategies
- Procurement of xylitol
- FDA IND application approval
- Recruitment and enrollment of subjects

REPORTABLE OUTCOMES: Provide a list of reportable outcomes that have resulted from this research to include:

- VA Research and Development Committee study approval
- UW HS IRB initial application study approval
- UW HS IRB continuing review study approval
- FDA IND application approval
- DHSC study approval
- Development of study tracking database

CONCLUSION: As stated, the purpose of this research effort is to evaluate the effects of two different types of nasal irrigation solution compared to a control group for sinus and fatigue symptoms in adults with GWI. While there have been inevitable practical and administrative hurdles, and the study team is new to research work within Veterans Administration structures, the study is open to enrollment and collecting high quality data. General success for either form of NI compared to routine care would provide an immediately accessible treatment to improve the quality of life of veterans with GWI, CRS and fatigue. Because of the likely overlap between the underlying etiologies of CRS and fatigue between GWI vets and the general population,

success may also translate to a more general population. Positive findings would suggest a number of important effects:

- Statistically positive results on HRQoL outcome measures would suggest that NI can provide effective adjunctive therapy for CRS and fatigue in adults with GWI, improving health of affected patients and potentially providing gains to society through reduced health care utilization and absenteeism related costs.
- Positive biomarker findings would contribute to our better understanding of the etiology of CRS and fatigue in the GWI population and of possible biological pathways underlying the NI efficacy.
- The finding that either form of NI is cost effective would provide economic justification for its clinical use.

REFERENCES: NA

APPENDICES:

Attachment A: UW HS IRB Initial Review approval

Attachment B: UW HS IRB Continuing Review approval

Attachment C: UW HS IRB Community Recruitment Initial Review approval

Attachment D: VA Research and Development Committee approval

Attachment E: Dupont Human Studies Committee study approval

Attachment F: FDA IND Acknowledgement



Health Sciences IRB

7/23/2012

Submission ID number: [2011-0843](#)

Title: Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness(GW100054)

Principal Investigator: DEAN KRAHN

Point-of-contact: DIANA MYERS

IRB Staff Reviewer: JENNIFER FENNE

The convened HS IRB conducted a full review of the above-referenced initial application. The study was approved for the period of 12 months with the expiration date of 6/18/2013.

To access the materials approved by the IRB, including any stamped consent forms, recruitment materials and the approved protocol, if applicable, please log in to your ARROW account and view the documents tab in the submission's workspace.

If you requested a HIPAA waiver of authorization, altered authorization and/or partial authorization, please log in to your ARROW account and view the history tab in the submission's workspace for approval details.

Prior to starting research activities, please review the Investigator Responsibilities guidance (<http://go.wisc.edu/m0lovn>.) which includes a description of IRB requirements for submitting continuing review progress reports, changes of protocol and reportable events.

Please contact the appropriate IRB office with general questions: Health Sciences IRBs at 608-263-2362 or Education Research and Social & Behavioral Science IRBs at 608-263-2320. For questions related to this submission, contact the assigned staff reviewer.



Health Sciences IRB

5/20/2013

Submission ID number: [2011-0843-CR001](#)

Title: Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness(GW100054)

Principal Investigator: DEAN KRAHN

Point-of-contact: DIANA MYERS

IRB Staff Reviewer: REBEKKAH WILLIAMS

The convened HS IRB conducted a full review of the above-referenced continuing review progress report. The study was approved for the period of 12 months with the expiration date of 5/19/2014.

NOTE: As previously communicated, please remember that the IRB expects that a change of protocol will be submitted as soon as possible to include the Xylatol IND in this protocol.

To access the materials approved by the IRB, including any stamped consent forms and recruitment materials, please log in to your ARROW account and view the documents tab in the submission's workspace.

Please review the Investigator Responsibilities guidance (<http://go.wisc.edu/m0lovn>), which includes a description of IRB requirements for submitting continuing review progress reports, changes of protocol and reportable events.

Please contact the appropriate IRB office with general questions: Health Sciences IRBs at 608-263-2362 or Education Research and Social & Behavioral Science IRBs at 608-263-2320. For questions related to this submission, contact the assigned staff reviewer.



Health Sciences IRB

7/1/2013

Submission ID number: [2012-1126](#)

Title: Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness - Community Recruitment

Principal Investigator: DAVID RABAGO

Point-of-contact: JESSICA GRETTIE

IRB Staff Reviewer: JOHN CEJKA

The convened HS IRB conducted a full review of the above-referenced initial application. The study was approved for the period of 12 months with the expiration date of 6/16/2014.

To access the materials approved by the IRB, including any stamped consent forms, recruitment materials and the approved protocol, if applicable, please log in to your ARROW account and view the documents tab in the submission's workspace.

If you requested a HIPAA waiver of authorization, altered authorization and/or partial authorization, please log in to your ARROW account and view the history tab in the submission's workspace for approval details.

Prior to starting research activities, please review the Investigator Responsibilities guidance (<http://go.wisc.edu/m0lovn>.) which includes a description of IRB requirements for submitting continuing review progress reports, changes of protocol and reportable events.

Please contact the appropriate IRB office with general questions: Health Sciences IRBs at 608-263-2362 or Education Research and Social & Behavioral Science IRBs at 608-263-2320. For questions related to this submission, contact the assigned staff reviewer.

**Department of
Veterans Affairs**

Memorandum

Date: July 16, 2012

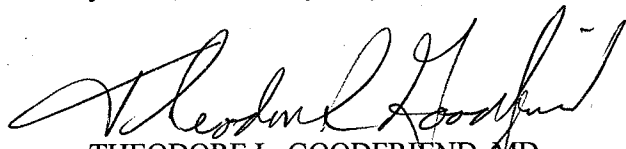
From: Associate Chief of Staff for Research

Subj: Research Protocol

To: Dean Krahn, MD, MS

1. Your protocol entitled "Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Syndrome" (UW HS IRB #H-2011-0843) was initially reviewed and endorsed by the VA Research and Development Committee on May 1, 2012 (pending HIPAA authorization revisions and IRB and PO approvals).
2. The HIPAA authorization has been revised as requested.
3. The Privacy Officer and the Information Security Officer have approved the protocol.
4. This protocol was approved by the UW Health Sciences IRB on June 22, 2012. Please provide my office with a copy of the date-stamped consent form, when available.
5. The protocol was re-reviewed by the R&D Committee on July 10, 2012. The Committee voted to approved the protocol contingent on revision of the Study Participant letters to be printed on VA letterhead and to include Dr. Krahn's name and signature line. Those revised letters have been received. You may now proceed with this research.
6. If this project requires access to patient charts or other confidential records, please make arrangements for such access with the VA Research Office. Only people who are VA employees or have gone through the VA WOC process are eligible for access to VA medical records.
7. An enrollment log is attached to this memo for your use in recording the names of VA subjects or volunteers enrolled in this study. You will be asked to update this log and send it to the VA Research Office (Rm. C-3127) quarterly. (If you wish to do this via e-mail, contact Bev Birdsall at 280-7007). If signed consent forms are required, we are also required to have a copy of the signed consent form in the Research Office for all VA subjects or volunteers enrolled in VA-approved studies. Send or deliver copies of the consent forms to Bev Birdsall, VA Research Office, Room C-3127.
8. The R&D Committee also approved the acceptance of any funding that may accompany this study. If you intend to have funds for this study deposited in a VA account, contact Marvin Rupp (ext. 17801) to make arrangements.

9. **Please remember** that you must enter a note in each subject's CPRS medical record when you obtain consent and before you begin the experiment. If you enter normal, non-VA subjects in your research study, they must also be entered into CPRS.



THEODORE L. GOODFRIEND, MD

Attachments: Investigator Responsibilities Related to VA Research and the Protection of Human Subjects
Enrollment log

cc: Dr. Rabago
Terry Little
Jamie Swanlund
UW HS IRB/ARROW



Integrated Health Services
1007 Market Street
Wilmington, DE 19898

August 13, 2012

TO: Anneli Tarpila, Ph.D.
Clinical Trial Manager,
Danisco Active Nutrition/Kantvik, DuPont Nutrition and Health

FROM: J. Morel Symons, Ph.D.
Chair, DuPont Human Studies Committee

RE: Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf War Illness

The DuPont Human Studies Committee (DHSC) has reviewed the proposed study by teleconference with the study investigators and business unit staff on 13 August 2012.

Based upon the teleconference and review of the following documents:

- DHSC Submission Form submitted by David Rabago, MD dated 31 May 2012
- The University of Wisconsin, Madison, Health Science IRB dated 23 July 2012
- VA Research Consent Form, version 1, dated 3 November 2011 with IRB approval notation stamp dated 19 June 2012
- Gulf War Veteran Experimental Treatment Flyer not dated
- Nasal Irrigation for Chronic Rhinosinusitis and Fatigue in Patients with Gulf Ware Illness Final and Approved Protocol not dated
- Biographical Sketch for Dr. Tony Kille
- Curriculum Vitae for Dr. David Rabago, Principal Investigator

The DHSC gives its approval for Active Nutrition/Kantvik to go forward with the proposed study.

In addition, during the conduct and completion of the study, please provide the DHSC with:

- Written notification of any adverse reactions or events and interim status reports as appropriate
- Notification when the study is complete with a copy of the executive summary of the final report
- Documentation that the trial has been registered with the U.S. National Institutes of Health (NIH) clinical trials database (<http://www.clinicaltrials.gov/>) or a similar clinical trial registry of the investigator's choice.

Regards,

A handwritten signature in black ink, reading "J Morel Symons". The signature is written in a cursive, flowing style.

J. Morel Symons, Ph.D.
Chair, DuPont Human Studies Committee



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116364

IND ACKNOWLEDGEMENT

University of Wisconsin, Department of Family Medicine
Attention: David Rabago, MD
1100 Delaplaine Court
Madison, WI 53711

Dear Dr. Rabago:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA). Please note the following identifying data:

IND NUMBER ASSIGNED: 116364
SPONSOR: David Rabago, MD
PRODUCT NAME(S): Xylitol
DATE OF SUBMISSION: August 20, 2012
DATE OF RECEIPT: September 4, 2012
INDICATION: Chronic Rhinosinusitis

You may not initiate studies in humans until 30 days after the date of receipt shown above unless we notify you sooner that you may proceed. If, on or before October 4, 2012, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will immediately notify you verbally or in writing that (1) clinical studies may not be initiated under this IND ("clinical hold") or (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). If we place your human studies on clinical hold, you will be notified in writing of the reasons and the information necessary to correct the deficiencies. In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have subsequently notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121

Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>.

Additional information regarding Title VIII of FDAAA is available

at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinfo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **IND 116364** submitted on August 20, 2012, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

ADDITIONAL IND RESPONSIBILITIES

As sponsor of this IND, you are responsible for compliance with the FDCA (21 U.S.C. §§ 301 et. seq.) as well as the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. A searchable version of these regulations is available at

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>. Your responsibilities include:

- Reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]. If your IND is in eCTD format, submit 7-day reports electronically in eCTD format. If your IND is not in eCTD format, you may submit 7-day reports by telephone or fax;

- Reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)]. If your IND is in eCTD format, submit 15-day reports to FDA electronically in eCTD format. If your IND is not in eCTD format, you may submit 15-day reports in paper format; and
- Submitting annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

We remind you that, under 21 CFR 312.8(a)(3), you may not charge for this investigational drug without prior written authorization from FDA.

GOOD LABORATORY PRACTICE

All laboratory or animal studies intended to support the safety of this product should be conducted in compliance with the regulations for "Good Laboratory Practice for Nonclinical Laboratory Studies" (21 CFR 58). If such studies have not been conducted in compliance with these regulations, provide a statement describing in detail all differences between the practices used and those required in the regulations.

ENVIRONMENTAL ASSESSMENT

Box 12, item 7 of form FDA 1571 requests that either an "environmental assessment," or a "claim for categorical exclusion" from the requirements for environmental assessment, be included in the IND. If you did not include a response to this item with your application, please submit one. Information on environmental assessments is available in the guidance "Environmental Assessment of Human Drugs and Biologics." This document is available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070561.pdf>.

SUBMISSION REQUIREMENTS

Cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate (original plus two copies). Please include three originals of all illustrations that do not reproduce well. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be

necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Susmita Samanta, MD, Safety Regulatory Project Manager at (301) 796-0803.

Sincerely,

{See appended electronic signature page}

Frances V. LeSane
Chief, Project Management Staff
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANCES V LESANE
09/21/2012